REMARKS

Claims 1-4, 9-12, and 28-37 are pending in the application. No new matter has been added.

Rejection of Claims 29, 31, and 37 under 35 U.S.C. § 112

Claims 29, 31, and 37 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention. Specifically, the Examiner alleges that the specification is not enabling because Applicant has not met the conditions that the PV1 antibody be known and readily available to the public or obtainable by a repeatable method set forth in the specification. The Examiner admits that the specification enables a skilled artisan to produce an anti-CD28 antibody and a corresponding scFv molecule, however, the Examiner alleges that "the molecule so obtained will not be the instantly recited RV1 (*sic*), because, as one of skill in the art is aware, each antibody is unique."

Applicants respectfully traverse this rejection. As a first matter, hybridoma cells, such as the PV1 cell line, produce a single type of antibody, called a monoclonal antibody - in this case, an IgG. The specific regions of an antibody that define its structure (*e.g.,* variable heavy (V_H) and variable light (V_L)) or function (*e.g.,* antigen-binding portion) have been extensively and precisely defined, and are thus well-known to one of skill in the art. The PV1 hybridoma has been deposited in the American Type Culture Collection (ATCC) under the terms and conditions of the Budapest treaty (see U.S. Patent No. 5,948,893, Col. 1), and is publicly available under ATCC Number HB-12352. Given this publicly-available hybridoma, a skilled artisan could readily use the detailed methods taught on pages 28-31 of the specification to produce the PV1 scFv. Furthermore, a skilled artisan could readily use methods known in the art at the time of filing, and outlined in the specific examples of U.S. Patent No. 5,948,893 (Cols. 11-16) and Abe *et al.* (*J Immunol*, 1995, 154: 985-997; submitted herewith as Appendix A) to produce the PV1 hybridoma. In light of all of the above, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 1-2, 9-10, and 32-33 under 35 U.S.C. § 102(b)

Claims 1-2 and 9-10 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Linsley *et al.* (U.S. Patent 5,521,288), as evidenced by Paul (*Fundamental Immunology*, 1999, p. 451), and as further evidenced by Beaudette-Zlatanova *et al.*[1] According to the Examiner, Linsley *et al.* explicitly teach that anti-CD28 antibodies can be used to treat insulin-dependent diabetes mellitus (column 36 lines 36-43). Furthermore, the Examiner is of the opinion that the claim language or limitations result in a manipulative difference in the method steps, when compared to the prior art disclosure. Lastly, the Examiner asserts that the enablement of prior art is evidenced by teachings of Beaudette-Zlatanova *et al.* (Am J. Transplant., 2006, 6: 857-858), who observed that two anti-CD28 monoclonal antibodies with different functional activities completely prevented diabetes in BBDP rats.

As the Examiner is aware, "[a] claim is only anticipated if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987), M.P.E.P. 2131. Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989), M.P.E.P. § 2131.

Applicants respectfully traverse the rejection and assert that the references cited by the Examiner do not teach each and every element of the claimed invention. The instant claims are drawn to methods of downmodulating an autoimmune response, an ongoing immune response, or a CD28-mediated interaction in a subject having type I diabetes, comprising administering an effective amount of an antigen-binding portion of an anti-CD28 antibody to the subject.

Linsley *et al.* disclose that mAB 9.3, an anti-CD28 antibody, is an inhibitor of an *in vitro* immune response that is dependent on the interaction of B7 and CD28. Accordingly, Linsley *et al.* performed *in vitro* experiments in various cell lines. Notably, Linsley *et al.* does not teach the use of anti-CD28 antibodies to treat insulin-dependent diabetes mellitus, as the Examiner alleges, but rather, lists the disease among several other unrelated diseases, including myasthenia

[1] The Examiner has cited the latter reference as (*Am. J. Transplant.*, 2006, 6: 857-858), however, Applicants respectfully point out that this citation is for an Editorial discussing the paper by Beaudette-Zlatanova *et al.*, for which the correct citation is: *Am. J. Transplant.*, 2006, 6: 894-902.

gravis, rheumatoid arthritis, and systemic lupus erythematosus. As stated in *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, F.3d 1051, 1054 (Fed. Cir. 2003), M.P.E.P. § 2121.01, "[t]he disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." Linsley *et al.* does not enable a method of downmodulating an immune or autoimmune response in a subject, let alone, a subject with type I diabetes. In short, Linsley *et al.* does not describe each and every element of the claimed method, and thus does not anticipate the pending claims.

Likewise, the Paul reference discloses the general properties of the CD28-mediated costimulatory pathway and does not make up for the deficiencies of Linsley *et al.* In contrast to the antibodies taught in the instant application, which function by blocking signaling through CD28, the only type of anti-CD28 antibody discussed by Paul is one that stimulates CD28-mediated signaling. Finally, Paul does not mention any immune system-related disorders or treatment of these disorders with anti-CD28 antibodies. Therefore, Paul does not prove enablement of Linsley *et al.* and provides no additional evidence to further support Linsley *et al.*

Moreover, contrary to the Examiner's assertion that enablement of prior art is evidenced by Beaudette-Zlatanova *et al.*, the results of Beaudette-Zlatanova *et al.* support Applicants' position that Linsley *et al.* does not enable methods of downmodulating an autoimmune response, ongoing immune response, or CD28-mediated interaction in a subject having type I diabetes, via administration of antibodies blocking CD28-mediated signaling. Rather than using an anti-CD28 antibody that blocks signaling via CD28, as claimed in the instant application, Beaudette-Zlatanova *et al.* use two antibodies that exert their effects via mechanisms distinct from blocking of CD28-mediated signaling. JJ316, a "super-agonistic" anti-CD28 antibody, stimulates CD28 signaling and induces the expansion of regulatory T cells. The JJ319 anti-CD28 antibody exerts its immunosuppressive effects by decreasing the amount of CD28 expressed on the surface of cells prepared from mesenteric lymph nodes (Dengler *et al.*, *Transplantation*, 1999, 67: 392-398). Thus, Beaudette-Zlatanova *et al.* does not prove enablement of the use of an anti-CD28 blocking antibodies *in vivo*, as taught in the instant application. Beaudette-Zlatanova *et al.* therefore provides no additional evidence to further support Linsley *et al.* In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of these rejections.

Rejection of Claims 1-4, 9-12, 28, 30, and 32-36 under 35 U.S.C. § 102(e)

Claims 1-4, 9-12, 28, 30, and 32-36 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Yu *et al.* (U.S. Patent Publication No. 2002/0006403), as evidenced by Paul (*Fundamental Immunology*, 1999, pg. 451), and as further evidenced by Beaudette-Zlatanova *et al.* (*Am J. Transplant.* 2006, 6: 894-902). The Examiner asserts that "Yu *et al.* teach that blocking antibodies can be used to treat autoimmune diseases, such as diabetes mellitus." The Examiner also alleges that Yu *et al.* have demonstrated that anti-CD28 antibodies are effective in downmodulating an immune response *in vivo* (*e.g.,* Example 3 at page 22). Furthermore, according to the Examiner, Yu *et al.* explicitly teach that blocking anti-CD28 antibodies can be used to treat autoimmune diseases, such as diabetes mellitus (see Summary of Invention at paragraphs 0010 - 0023, and in particular paragraph 0013).

As the Examiner is aware, "[a] claim is only anticipated if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), M.P.E.P. § 2131. Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989), M.P.E.P. § 2131.

Applicants respectfully traverse the rejection. As set forth above, the claims of the present invention are drawn to methods of downmodulating an autoimmune response, ongoing immune response, or CD28-mediated interaction in a subject having type I diabetes, via administration of anti-CD28 blocking antibodies.

Yu *et al.* discloses that an anti-CD28 antibody prevents graft-versus-host disease (GVHD). While Yu *et al.* generally suggests that anti-CD28 antibodies may be used to treat other immune related disorders, it merely names type I diabetes in a laundry list of several other unrelated diseases, including psoriasis, multiple sclerosis, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, dermatomyositis, polymyositis, Sjogren syndrome, polyarteritis nodosa, and vasculitis, and does not provide an enabling disclosure. As stated in *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, F.3d 1051, 1054 (Fed. Cir. 2003),

M.P.E.P. § 2121.01, "[t]he disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." One of skill in the art would appreciate that there is no basis for extrapolating results from GVHD to an autoimmune disease, such as type I diabetes. As discussed in Bolton & Bradley (*Am. J. Transplant.* 2006, 6: 857-858; submitted herewith as Appendix B), treatments that are effective for certain immune-related disorders may be ineffective for others. In this Editorial, the authors discuss the failure of treatment with CTLA4-Ig to inhibit the development of disease in any of three experimental models of diabetes. In one model, treatment with CTLA4-Ig accelerated the onset of the disease. This is despite the fact that "CTLA4-Ig is effective in preventing pathology in several other models of autoimmune disease." These results show the inherent inaccuracy in extrapolating treatment efficacy even within a disease class. The inaccuracy in extrapolating between disease classes (*i.e.,* GVHD to autoimmune), as Yu *et al.* suggests, is expected to be even greater. Furthermore, Yu *et al.* does not anticipate methods of downmodulating an immune response in a subject with type I diabetes, as claimed in the instant application. In light of the above, the general suggestion of treating diabetes made by Yu *et al.*, after acquiring data pertaining to GVHD, is not enabling and thus Yu *et al.* do not describe all elements of the claimed method.

Likewise, the Paul reference discloses the general properties of the CD28-mediated costimulatory pathway. In contrast to the antibodies taught in the instant application, which function by blocking signaling through CD28, the only type of anti-CD28 antibody discussed by Paul is one that stimulates CD28-mediated signaling. Finally, Paul does not mention any immune system-related disorders or treatment of these disorders with anti-CD28 antibodies. Therefore, Paul does not prove enablement of the Linsley reference and provides no additional evidence to further support Linsley *et al.*

Moreover, contrary to the Examiner's assertion that enablement of prior art is evidenced by Beaudette-Zlatanova *et al.*, the results of Beaudette-Zlatanova *et al.* support the Applicants' position that Linsley *et al.* does not enable methods of downmodulating an autoimmune response, ongoing immune response, or CD28-mediated interaction in a subject having type I diabetes, via administration of antibodies blocking CD28-mediated signaling. Rather than using an anti-CD28 antibody that blocks signaling via CD28, as claimed in the instant application,

Beaudette-Zlatanova *et al.* use two antibodies that exert their effects via mechanisms distinct from blocking of CD28-mediated signaling. JJ316, a "super-agonistic" anti-CD28 antibody, stimulates CD28 signaling and induces the expansion of regulatory T cells. The JJ319 anti-CD28 antibody exerts its immunosuppressive effects by decreasing the amount of CD28 expressed on the surface of cells prepared from mesenteric lymph nodes (Dengler *et al.*, *Transplantation*, 1999, 67: 392-398). Thus, Beaudette-Zlatanova *et al.* does not prove enablement of the use of an anti-CD28 blocking antibodies *in vivo*, as taught in the instant application. Beaudette-Zlatanova *et al.* provides no additional evidence to further support Linsley *et al.* In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of these rejections.

CONCLUSION

In view of the foregoing remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-832-1000. The Commissioner is authorized to charge any underpayments, or to credit any overpayment, to Deposit Account No. **06-1448, reference WYS-007.01.**

Respectfully submitted,
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